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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,996	10/17/2003	Lothar Steidler	2676-6096US	1934

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
03/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/687,996	STEIDLER, LOTHAR	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,10-15,17-19,21-26,29-35,37-39,42 and 65-68* is/are pending in the application.

4a) Of the above claim(s) *11,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,10,12,13,15,17,21-26,29-32,34,35,37-39,42 and 65-68* is/are rejected.

7)☒ Claim(s) *14, 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/08 has been entered.

Claims 4, 8, 9, 16, 20, 27, 28, 36, 40, 41, and 43-64 have been canceled. Claims 1-3, 5-7, 10-15, 17-19, 21-26, 29-35, 37-39, 42, and newly presented claims 65-68 are at issue and are present for examination.

Claims 11, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on March 30, 2006.

Claim 14 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim (Note claim 14 depends from claim15 which is also a multiply dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim 34 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 34 does not further limit claim 32 as the process recited in claim 32 recites a gene disruption process.

Claims 22, 32 and 67 are objected to because of the following informalities: the word gene should be inserted following "in an inactive thymidylate synthase" in claim 22, the word "is" should be inserted prior to "produced by a process" in claim 32 and "integrated" is misspelled in claim 67. Appropriate correction is required.

Claims 1-3, 5-7, 10, 12, 13, 15, 17, 22, 31, 65, and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 22, 31 and 68 (upon which claims 2, 3, 5-7, 10, 12, 13, 15, 17, and 65 depend) are confusing in the recitation of "said strain" as it is unclear if this refers to the *thyA* mutant strain or the parent *Lactococcus* strain prior to mutation.

Claims 5 and 65 (upon which claims 6, 7, 10, 13, 15, 17, and 68 depend) are confusing in the recitation of "further transformed as the *thyA* mutant strain of claim 1 is not recited as a transformed strain. Thus it is not clear how it can be "further transformed".

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel organism, i.e., *L. lactis* strain MG1363. Since the organism is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed organism has been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. ∋ 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the organism and it is not apparent if it is readily available to the public. Accordingly, it is deemed that a deposit of this organism should have been made in accordance with 37 CFR 1.801-1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit is not made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;
2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become inviable.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 10, 12, 13, 15, 17, 21, 23-26, 29, 30, 32, 34, 35, 37-39, 42, and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al. (WO00/01799) in view of Steidler et al. (WO00/23471) and Curtiss III (US Patent 4,888,170).

Nilsson et al. teach a *thyA* mutant strain of *Lactococcus lactis* strain CHCC373 in which the chromosomal thymidylate synthase gene was replaced by a mutant gene containing a deletion of the 3' end of the promoter and the 5' end of the coding sequence of the endogenous thymidylate synthase gene of this strain by homologous recombination. The *thyA* mutant strain of Nilsson et al. is a thymidine auxotrophic strain. Although the sequence of the flanking regions of the thymidylate synthase gene are not given in Nilsson et al. they are inherently present within the strain and in view of the fact that it is a strain of *Lactococcus lactis* the sequences of these regions will clearly be highly similar to SEQ ID NOS:1 and 2 and will include regions of 100 or more nucleotides with 90% or more identity to SEQ ID NOS:1 and 2. The *thyA* mutant strain of Nilsson et al. differs from that claimed in that it does not comprise a heterologous gene encoding a therapeutic protein.

Steidler et al. teach a transformed *Lactococcus lactis* strain which produces IL-10 and the oral administration of this strain to animals for delivery of the IL-10 to the intestinal mucosa of the animal.

Curtiss III teach that for administration of genetically engineered bacteria that are intended to produce a heterologous protein in the intestinal mucosa of the animal alteration of the

microorganism such that it is incapable of surviving in nature but still capable of delivering the heterologous protein to the intestinal mucosa is preferable and that alteration of *E. coli* strains to preclude their survival in nature is well-known and the same deletion mutations (e.g., .ΔthyA) used in the laboratory to create bacteria that require a particular nutrient can be used to create avirulent carrier microbes incapable of long-term survival without preventing penetration of Peyer's patches. (see particularly column 9, lines 4-48). Curtiss III further show that following administration of several such *thyA* mutants to mice, that a 5-fold increase in the titer of the microorganisms can be detected in the intestinal mucosa and that the heterologous proteins were clearly produced.

Therefore, it would have been obvious to one of ordinary skill in the art to use the *thyA* mutant strain of *Lactococcus lactis* of Nilsson et al. for the therapeutic delivery of a heterologous protein such as the IL-10 of Steidler et al. as Steidler et al. teach the use of *Lactococcus lactis* strains for the delivery of this protein to the intestinal mucosa. One of skill in the art would have been motivated to select the *thyA* mutant strain of *Lactococcus lactis* of Nilsson et al. as the host strain for the therapeutic delivery by the disclosure of Curtiss III that for administration of genetically engineered

bacteria that are intended to produce a heterologous protein in the intestinal mucosa of the animal alteration of the microorganism such that it is incapable of surviving in nature but still capable of delivering the heterologous protein to the intestinal mucosa is preferable and the *thyA* mutant strains are examples of such strains. Furthermore, while Steidler et al. do not teach insertion of the heterologous IL-10 sequence into the *Lactococcus lactis* by integration of the IL-10 sequence into the chromosome of the bacterium one of skill in the art would understand that any common method of introducing a heterologous gene into a bacterium could be used and the use integration in the chromosome is known in the art to have the advantage of not requiring an antibiotic marker to stably maintain the heterologous gene. As the vector of Nilsson et al. used for introduction of the mutant *thyA* mutant strain is designed for replacement of the endogenous thymidylate synthase gene with the mutant *thyA* gene it would have been obvious to one of skill in the art to insert the heterologous IL-10 expression cassette in between the two *thyA* gene fragments of the vector of Nilsson and then to replace the endogenous gene with the *thyA*/IL-10 cassette.

Claim 33 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent

form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652